REMARKS

Status of the Claims

Claims 5, 6, 20 and 21 are pending as shown above.

35 U.S.C. 103(a)

The rejection of the claims under 35 U.S.C. § 103(a) as allegedly obvious over Pomerantz (1988) *Biochemistry* 37(4):965-970 (hereinafter "Pomerantz") in view of Krylov et al. (1994) *EMBO J.* 13(12):2849-2861 (hereinafter "Krylov") was reiterated by the Examiner. (Office Action, pages 2-9). Pomerantz was cited for allegedly disclosing a zinc finger protein fused to a naturally occurring dimerization domain extracted from the GAL4 protein and for suggesting the use of non-naturally occurring dimerization domains. *Id.* Krylov, reference 19 of Pomerantz, was cited for demonstrating that non-naturally occurring peptide linkers could be utilized to complex zinc finger proteins. *Id.*

In response to Applicants' arguments, it was again asserted that Pomerantz teaches "fusion" of zinc finger proteins with short peptide linkers for covalent linkages, which makes it obvious (predictable) to use such linkers for non-covalent linkages and that the "art appreciates the use or teaches the conventionality of a short length peptide linker to link two proteins whether by covalent or non-covalent linkage." (Final Office Action, page 5). In addition, it was again asserted that the paragraph bridging pages 965-966 of Pomerantz suggests fusion of heterologous modules with a short peptide linker. (Final Office Action, pages 6-7). The Examiner also cites the specification in asserting that naturally-occurring dimerization domains render the claimed non-naturally occurring peptides obvious. (Final Office Action, pages 8-9).

With regard to Krylov's failure to teach dimerization domains under 30 amino acids, the Examiner asserted that "there is nothing in the specification that demonstrates that the claimed 30-residue peptide produces new or unexpected results from that of Krylov, 32-residue." (Final Office Action, pages 10-11, citing *Merck v. Biocraft* and *KSR v. Teleflex*.

Contrary to the Examiner's assertions, an obviousness rejection cannot be sustained where the references fail to teach the claimed elements and where the suggested modification is not a predictable use of known elements. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398; 82 USPQ2d 1385, 1397 (2007) and Patent Office Guidelines regarding determining obviousness

issued in view of *KSR*, an obviousness rejection is only proper when the proposed combination of elements results in a predictable outcome (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007, emphasis added):

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

Rather, the Supreme Court in *KSR* reiterated that an obviousness inquiry is fact-dependent and that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 82 UPSQ2d at 1389. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

For the reasons of record and reiterated herein, Pomerantz and Krylov both fail to teach the claimed elements. Specifically, neither document teaches or suggests zinc finger protein-containing fusion proteins linked to each other by non-naturally occurring dimerizing peptides of 30 amino acids or less in length. Rather, Pomerantz uses the naturally occurring GAL4 dimerization domain, which is approximately 50 amino acid residues in length. This is not a non-naturally occurring dimerization domain of 30 or fewer amino acid residues, as claimed.

Further, as admitted, Krylov's "dimerization" element is also over 30 amino acid residues, namely 32 residues in total. Moreover, Krylov does not disclose a zinc finger complex, but, instead, relates to mutation of certain amino acid residues of naturally occurring leucine zipper proteins (Krylov, left column of page 2850 to left column of page 2851 and Fig. 1):

> The protein sequence of the first four leucine zipper heptads of the host or parent protein, the bZIP protein VBP (Iyer et al., 1991) is presented in Figure 1B.
> ....
> The lower section of Figure 1B presents the nomenclature used to describe our various mutant proteins.

Clearly, Krylov's leucine zipper dimerization mutants are not used to link heterologous zinc finger proteins and are not non-naturally occurring dimerizing peptide, as claimed.

Thus, Pomerantz and Krylov fail to disclose the claimed elements, individually or in any combination. As such, the claimed subject matter (e.g., non-naturally occurring dimerization peptides of 30 amino acids or less) is not made up of known elements disclosed in the references. Accordingly, a *prima facie* case of obviousness has not been (and cannot be) established.

In addition, the Examiner's assertion that the claimed non-naturally occurring dimerizing peptides are somehow predictable from Pomerantz and Krylov is also in error. In particular, the Examiner has again misinterpreted the teachings of Pomerantz, arguing that the skilled artisan reading Pomerantz would view short covalent peptide linkers and longer dimerization domain linkers as interchangeable in terms of linking of zinc fingers. This assertion is in error. As would be apparent to the skilled artisan, the "shorter" linkers disclosed in Pomerantz are made up of a single peptide that links one zinc finger to the adjacent zinc finger. This is entirely unlike the claimed molecules in which two dimerization domains (one per zinc finger protein) interact to link the zinc finger proteins. Accordingly, the skilled artisan would not find short, covalent linkers to predictably act as dimerization elements.

Pomerantz also clearly teaches away from the interchangeability of covalent (short) peptide linkers and long, naturally occurring dimerization domains in terms of linking zinc finger proteins. Rather, Pomerantz teaches the use of long, naturally occurring dimerization domains and short covalent peptides are alternatives to each other, which is the opposite of interchangeability (Pomerantz, page 966, emphasis added; also cited on page 6 of the Final Office Action):

> Dimer formation, frequently employed by **natural** DNA-binding proteins to enhance the affinity and specificity of recognition, provides **another** attractive design strategy. The capacity for homo- and heterodimerization offers several potential advantages for DNA binding proteins. ... Design strategies that employ dimerization also **may provide a useful alternative to the covalent linkage of multiple DNA-binding domains**. Large covalent assemblies might have higher absolute affinity for non-specific DNA sites and might become kinetically trapped at inappropriate sites in the genome. Dimerization provides **an alternative way** of bringing multiple domains together as a functional unit.

Therefore, Pomerantz is clear that any predictability in linking via dimerization lies in the use of naturally occurring dimerization domains of at least 50 amino acid residues. Pomerantz doesn't teach that short linkers dimerize, as would be required to show obviousness. This reference only teaches that short (covalent) linkers can be used to fuse zinc finger proteins and that, as an alternative to these covalent linkers, long, naturally occurring dimerization domains can be used. Pomerantz teaches nothing about the "predictability" of using short linkers as dimerizing peptides because it was not even contemplated that they would use anything other than the long naturally occurring dimerization domains known in the art. As short dimerization peptides were not known elements and as it is not even contemplated to use non-naturally occurring dimerization peptides of 30 or fewer amino acids in length in the reference, it cannot be a predictable use of known elements and the obviousness rejection cannot stand.

Likewise, Krylov's dimerization domains (which notably are not isolated from the context of the leucine zipper protein as a whole) are also acknowledged to be over 30 amino acids in length. Contrary to the Examiner's assertions, it is both new and surprising that non-naturally occurring dimerization domains of 30 (or less) amino acids could be used as functional dimerization elements. Furthermore, Krylov does not in any way teach that it is a predictable use of leucine zipper dimerization domains to join zinc finger proteins. As noted above and repeatedly on the record, Krylov relates solely to mutation of certain amino acid residues of naturally occurring leucine zipper proteins and teaches nothing about using dimerization elements out of the context of leucine zipper proteins as a whole to link zinc finger protein fusion proteins. Therefore, as with Pomerantz, Krylov does not establish that it was a predictable use of (mutated) leucine zipper proteins to link zinc finger proteins to each other and the obviousness rejection is improper.

The obviousness rejection is also improper because modifying the references as suggested would destroy their intended functions. It is axiomatic that an obviousness rejection is improper where the proposed modification would destroy the intended function of the reference (see, e.g. *In re Fritch* 23 USPQ2d 1780, 1783, n.12 (Fed. Cir. 1992) and *In re Ratti* 123 USPQ 349, 352 (CCPA 1979)):

> A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.
>
> [I]t would require a substantial reconstruction and redesign of the elements shown in [a cited reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate.

In the instant case, the proposed modifications to Pomerantz and Krylov would require a change in the basic principles under which the references' proteins were designed to operate. Specifically, modifying Pomerantz as suggested would destroy the intended function of using long (50 amino acid), naturally occurring dimerization domains instead of short covalent linkers. Similarly, modifying Krylov to take long (at least 32 amino acids) domains out of the context of remainder of the protein would destroy the reference's intended function of dimerizing leucine zipper proteins.

For all of the aforementioned reasons, the rejection under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Applicants believe that the claimed subject matter is now in condition for allowance and early notification to that effect is respectfully requested. If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned.

Please address all correspondence to the undersigned.

Respectfully submitted,

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